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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,103	07/05/2002	Sandrine Lentsch Graf	01-1081	4719

20306 7590 03/15/2005

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,103	GRAF ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 4, 2004 has been entered.

2. Applicant's amendment is acknowledged. Claim 1 has been amended.

3. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejection Withdrawn

4. In view of Applicant's amendment and response the rejection of claims 9 and 10 under 35 U.S.C. 102/103 set forth on pages 4-5, paragraph 5 of the previous Office Action is withdrawn.

Rejections Maintained

5. The rejection of claims 1-4 under 35 U.S.C. 102(e) is maintained for the reasons set forth on pages 2-3, paragraph 4 of the Final Office Action.

The rejection is on the grounds that LaPosta et al teach a liquid vaccine composition comprising a polysaccharide covalently bound to a protein (column 4, lines 60-65). LaPosta et al teach that sugars such as trehalose may be added to the vaccine composition to prevent aggregation (i.e. stabilize) of the vaccine composition (column 3, lines 10-26). LaPosta et al anticipate the claimed invention. LaPosta et al teach suitable antigens used in the vaccine include antigens from *Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae*, Group A *Streptococcus* and Group B *Streptococcus* (column 4, lines 25-64). LaPosta et al teach that the antigens of the invention, for example, bacterial capsular polysaccharide or a fragment thereof is chemically linked to a protein carrier molecule in order to enhance immunogenicity (column 4, lines 60-64). LaPosta, et al anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine and the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that LaPosta et al do not anticipate the claimed invention. Applicant urges that claim 1 has been amended to recite that the addition of the trehalose to the polysaccharide-protein preserves immunogenicity and LaPosta et al fail to teach these limitation. Applicant urges that LaPosta et al fail to teach or suggest that trehalose is more effective than other sugars such as lactose at preserving the immunogenicity of the composition over time.

Applicant's arguments filed November 4, 2004 have been fully considered but they are not persuasive. LaPosta et al teach a liquid vaccine composition

comprising a polysaccharide covalently bound to a protein. Although, the claim limitation "wherein in the immunogenicity of the protein linked polysaccharide in the composition is preserved to a greater extent over time as compared to the immunogenicity of the protein linked polysaccharide in a corresponding vaccine composition not containing trehalose" is a limitation of intended use, LaPosta et al teach that the addition of sugar (including trehalose) solves the problems of settling out and aggregation problems of the prior art. Therefore, the trehalose added to the vaccine composition of the prior art would "preserve the immunogenicity of the vaccine composition to a greater extent over time" to the same degree as the claimed composition comprising trehalose. Applicant has provided no side-by-side comparison to show that the claimed vaccine compositions differ from that of the prior art. Therefore, it is the Examiner's position that the vaccine compositions as taught by LaPosta et al anticipate the claimed invention.

6. The rejection of claims 1-8 and 11-16 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 5-7, paragraph 6 of the previous Office Action.

The rejection was on the grounds that Anderson et al teach vaccine comprising covalent attachment of capsular polymer fragment derived from bacterial capsular polymers to bacterial toxoids (column 2, lines 58-64). Anderson et al teach that suitable carrier proteins of the inventions include diphtheria and tetanus toxoids (columns 5, lines 29-36). Anderson et al teach that vaccine of the invention include vaccines against systemic infections caused by the pathogens *Haemophilus influenzae* type b, *E. coli*, pneumococcus, meningococcus, streptococcus and pseudomonas (column 6, lines 59-65). Anderson et al teach that the regulation of any reaction parameter, e.g. time,

temperature, pH, etc. which affects the reactivity or rate of reaction will alter the final composition and structure of the conjugate (column 4, lines 45-49). Anderson et al teach that the vaccines of the invention have been lyophilized (column 18, lines 35-40). Anderson et al teach that the conjugates of the invention appear to convert into macromolecular aggregates after preparation (column 13, lines 67-68 and column 14, lines 1-2).

Anderson et al do not teach the use of trehalose.

Roser et al teach the use of trehalose as a means of protecting substances such as vaccines from aggregation (see the Title and the Abstract). Roser et al teach that the addition of trehalose to biologically active substances can reduce aggregation during dehydration and rehydration (page 4). Roser et al teach that the addition of trehalose prevents the formation of all multimeric forms of the substance (page 5). Roser el al teach the addition of trehalose in the amount of about 1% to 50% more preferably about 5% to 25% to biologically active substances (page 7). Roser et al teach that material dried in the presence of trehalose, when resuspended produces a smooth and single particulate suspension (page 9).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the trehalose as taught by Roser et al to the immunogenic conjugate vaccines of Anderson et al because Roser et al teach the use of trehalose as a means of protecting substances such as vaccines from aggregation and Roser et al also teach that the addition of trehalose prevents the formation of all multimeric forms of the substance. It would be expected barring evidence to the contrary that vaccine comprising trehalose would retain their stability in long-term storage.

Applicant urges that to establish a *prima facie* case of obviousness, all claim limitations must be either taught or suggested by the prior art. Applicant urges that Anderson et al nor Roser et al teach a composition comprising trehalose and a polysaccharide-protein that preserves the immunogenicity of the polysaccharide-protein over time. Applicant urges that Anderson et al teach that the aggregates formed "presumably by cross-linking from the formalin treatment" and Anderson et al do not teach or suggest the use of trehalose to prevent cross-linking of the immunogenic conjugates. Applicant urges that Roser et al teach that prevention of protein aggregates using trehalose is important as protein

aggregates induce an "unwelcome" immune response and therefore Roser et al teach that is desirable to decrease the immungenicity of compositions containing proteins. Applicant urges that Roser et al do not disclose, teach or suggest the use of trehalose to prevent aggregation of substances outside the dehydration/rehydration or freezing /thawing contexts. Applicant urges that with such a disclosure, one of skill in the art would not be motivated to combine Anderson et al with Roser et al.

Applicant's arguments filed November 4, 2004 have been fully considered but they are not persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Anderson et al teach polysaccharides conjugated to carrier proteins and teach these conjugates can be lyophilized. While it is true that Anderson et al do not teach adding trehalose to immunogenic conjugates, however, Roser et al teach the addition of trehalose prior to freezing or dehydrating. Therefore, Roser et al teach the addition of trehalose to composition in the liquid state not merely in the context of freezing and thawing or dehydration. One of ordinary skill in the art would be motivated to combine the teachings of the prior art because Roser et al teach that the addition

of trehalose to protein compositions prevent degradation of proteins when reconstituted. To address Applicant's comments regarding the prior art teaching that prevention of protein aggregates using trehalose is important as protein aggregates induce an "unwelcome" immune response and therefore the prior art teaches that is desirable to decrease the immungenicity of compositions containing proteins, the Examiner disagrees with Applicant's interpretation of this statement. It is the Examiner's position that Roser makes this statement to show that protein compositions that contain trehalose prevents aggregation of proteins and thereby makes a more stable composition. One of ordinary skill in the art can reasonably conclude that compositions that contain trehalose prevent aggregation and therefore "preserve the immunogenicity" of the protein or polysaccharide-protein over time thereby making a more effective composition. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 9-13 and 16 are rejected under 35 U.S.C. 103(a) as unpatentable over Roser et al *(US Paten No. 6,190, 701 B1 published February 20, 2001)* in view of LaPosta et al *(U.S. Patent No. 6,306,404 B1 published October 23, 2001).*

Claims 9-13 and 16 are drawn to a method of preserving the immunogenicity over time of a Liquid vaccine composition comprising at least one antigen consisting of a polysaccharide bound to a carrier protein, wherein the method comprises adding trehalose to the vaccine composition, and maintaining the vaccine composition in a liquid state.

Roser et al teach a method of preserving a stable liquid composition using trehalose (see the Title, the Abstract and columns 6-7). Roser et al teach the use of trehalose in these compositions at about 10% w/v (see Example 7) which meets the claim limitation "where in the quantity of trehalose to be added is between 3 and 12% by mass".

Roser et al do not teach capsular polysaccharides *Haemophilus influenzae* or polyribosylribitol phosphate or pneumococcal or meningococcal polysaccharides.

LaPosta et al teach a method of stabilizing a liquid vaccine composition comprising at least one antigen consisting of a polysaccharide bound to a carrier protein, wherein it consists in adding trehalose to the vaccine composition by teaching that sugars such as trehalose may be added to the vaccine composition to prevent aggregation (i.e. stabilize) of the vaccine composition (column 3, lines 10-26). LaPosta et al teach suitable antigens used in the vaccine include

antigens from *Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae*, Group A *Streptococcus* and Group B *Streptococcus* (column 4, lines 25-64). LaPosta et al teach that the antigens of the invention, for example, bacterial capsular polysaccharide or a fragment thereof is chemically linked to a protein carrier molecule in order to enhance immunogenicity (column 4, lines 60-64).

It would have been *prima facie* obvious at the time the invention was made to the add specific quantities (between 3-12 %) of trehalose to the vaccine compositions of LaPosta et al because Roser et al teach that the addition of specific quantities of trehalose would be effective in stabilizing injectable liquid compositions. It would be expected barring evidence to the contrary that vaccine comprising trehalose would retain their stability in long-term storage.

Status of Claims

8. No claims allowed.

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Biotechnology Patent Examiner
February 21, 2005

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